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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/647,457 | 11/29/2000 | Meir Shinitzky | 24390 | 6935 |

20529 7590 07/16/2002

NATH & ASSOCIATES
1030 15th STREET
6TH FLOOR
WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| TURNER, SHARON L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | |

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/647,457 | SHINITZKY ET AL. | |
| | Examiner | Art Unit | |
| | Sharon L. Turner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8 and 10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-14* is/are rejected.

7)☒ Claim(s) *3,5-8 and 10-127* is/are objected to.

8)☒ Claim(s) *1-8 and 10-14* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5.5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restriction*

Applicant's election with traverse of Group I, claims 1-6, 8, 10-11 and 13-14 in part to the extent drawn to the technical feature of SEQ ID NO:2 in Paper No. 10 (4-29-02) is acknowledged. It is noted that claims 7 and 12 have now been presented as a part of the invention of Group I, drawn to SEQ ID NO:2. The traversal is on the ground(s) that there is no appropriate explanation of serious burden. Applicants submit that there is no serious burden because a search of any one of the inventions would requires searching areas appropriate to the other inventions and further because Applicants would be forced to pay further fees for search and examination of the additional inventions. This is not found persuasive because as previously set forth the technical features differ in sequence structure, function, effects and are capable of distinct utilities. There is extensive search burden in examining all the inventions in a single application because the search for any one group is not co-extensive with a search for any other group, in particular the sequence searches are different for each invention. The fee structure has been determined by the Office to be appropriate compensation for the burden of search and examination of alternative inventions.

The requirement is still deemed proper and is therefore made FINAL.

### *Specification*

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The brief description of the drawings for Figures 1 and 2 should be amended to reflect the views, ie., Fig. 1A and 1B.

***Claim Objections***

Claims 3, 5, 6, 10 and 11 are objected to as reciting an improper Markush Group.

M.P.E.P. 803.02 states that:

> "Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

In instant case the technical feature polypeptides lack unity because they fail to share the same structural features.

Claims 3, 5, 6, 10 and 11 are also objected to because the claims are drawn in part to non-elected inventions. Appropriate correction is required.

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. .The term "having" is equivalent to "comprising". Claim 10 does not further limit the subject matter of claim 8 which is already limited to a peptide having the sequence of SEQ ID NO:2.

Claim 6 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 7. When two claims in an application are duplicates or else are so close in

content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In as much as a patent is supposed to be limited to only one invention or, at most, several closely related indivisible inventions, limiting an application to a single claim, or a single claim to each of the related inventions might appear to be logical as well as convenient. However, court decisions have confirmed applicant's right to restate (i.e., by plural claiming) the invention in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough. Nevertheless, when two claims in an application are duplicates, or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other claim under 37 CFR 1.75 as being a substantial duplicate of the allowed claim.

In instant case claim 7 appears to additionally recites inherent properties of the peptides which consists of SEQ ID NO:2. While such provides the reader with additional information concerning the peptide, the recitations are not deemed to change the scope in any way. Thus, the claims are deemed duplicates.

Claims 8 and 10 and claims 11 and 12 are also objected to under 37 CFR 1.75 as being substantial duplicates. Claim 8 is directed to the assay wherein the peptide has the sequence of SEQ ID NO:2 and claim 10 is directed to the same assay wherein the peptide comprises the sequence of SEQ ID NO:2. As the term "having" is equivalent to "comprising" the claims are considered duplicates as there is no difference in scope between the peptides. Similarly, claims 11 and 12 are drawn to the assay wherein the peptide "is" or "consist(s)ing of" SEQ ID NO:2 and thus, there is no difference in scope between the peptide which "is" or "consist(s)ing of" SEQ ID NO:2.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed invention fails to reflect the hand of man in that it is directed to a product of nature. The claims should be amended to reflect an isolated peptide.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In the decision of *The Regents of the University of California v. Eli Lilly and Company,* 43 USPQ2d 1398 (CAFC 1997), the court held that:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of

> ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood , 107 F.3d at 1572, 41 USPQ2d at 1966.

Claim 1 is drawn to peptides which bind antibodies that are found in elevated levels in body fluids of schizophrenic patients. However, the specification only discloses 5 such peptides, as disclosed at p. 14, which bind to autoantibodies elevated in schizophrenic patients. These peptides are Glyceraldehyde-6-phosphate dehydrogenase, Enolase, Keratin, Hepatocyte growth factor and Extracellular calcium sensing receptor. While the artisan would recognizes that any 5 mer of these peptides may be capable of reacting with such antibodies, the artisan is not apprised nor does the specification teach alternative peptide sequences which would react with autoantibodies which are elevated in schizophrenic patients.

Further the specification at p. 17 exemplifies that based on the epitopes of the aforementioned proteins various related peptide sequences were generated and tested for binding to antibodies elevated in schizophrenic patients. As disclosed in Table 2, the peptides of SEQ ID NO's 1-8 exhibited activity whereas the peptides of SEQ ID NO's 9-14 did not. Table 2 is supportive of a written description of SEQ ID NO's 1-8 which sequences are within the scope of the invention.

With the exception of those peptides which are contiguous epitope segments of the disclosed peptides or are exemplified by SEQ ID NO:'s 1-8 of instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic and amino acid sequences and therefore conception is not achieved until

reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and/or amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Whereas the instant specification provides a detailed description of a number of species of peptides, the description is not sufficient to provide for those unrelated peptide epitopes which can not be predicted, are not disclosed but which are instantly claimed.

Claims 1, 4, 8 and 10-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for contiguous epitope segments of the disclosed peptides Glyceraldehyde-6-phosphate dehydrogenase, Enolase, Keratin, Hepatocyte growth factor, Extracellular calcium sensing receptor and for peptides of SEQ ID NO's:1-8 which are capable of binding to platelet derived autoantibodies which

are found to be elevated levels in schizophrenic patients, does not reasonably provide enablement for alternative, unrelated peptide sequences, for peptides which bind antibodies elevated in body fluids of schizophrenic patients, for peptides of the subgenus which bind antibodies capable of binding to SEQ ID NO:2, but are not capable of binding for example to SEQ ID NO's: 9-14 or for methods of assaying and kits for the detection and diagnosis of schizophrenia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability in the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000, Abstract and Box 2. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition. The

skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein targeted, see in particular Immunogenicity and Antigenic Specificity in Basic and Clinical Immunology, Ed. By Stites and Terr, Appleton Lange, Norwalk, Conn., 1991, pp. 101-108.

It is noted that the specification teaches particular peptides which as set forth above clearly exhibit binding to antibodies elevated in schizophrenic patients, see for example SEQ ID NO's:1-8. However, Table 2, clearly exemplifies that even amongst such highly conserved sequences as exemplified by SEQ ID NO's:9-14, which retain contiguous segments greater than 4-6 residues in length, even single amino acid differences can abrogate binding. This may be due to the particular antigenicity of the peptide used to produce the antibody, or due to the antibodies ability to recognize the particular three dimensional structure of the peptide. Regardless of the underlying reasons, it is clear that peptide/antibody interactions are unpredictable in the art. Yet, nonetheless the artisan would expect that peptides sharing at least contiguous epitopes of 4-6 amino acids in length would bind to antibodies generated via immunization to that peptide and such experimentation would not be undue.

However, what the artisan would not expect, is that particular peptides sharing such contiguous segments would not share antibody reactivity to a peptide so similarly made or to an antibody known to be reactive with such similar sequences. In essence the population of peptides which could bind an antibody capable of binding to SEQ ID NO:2, but not bind to SEQ ID NO's:9-14 would only be isolatable via screening and testing each immunogen/antigen/antibody possibility. Even so, the artisan could not be

sure until isolation, that such a peptide even exists. What applicant's have shown is that an autoantibody isolated from schizophrenic patients reacts with SEQ ID NO's:1-8 but not 9-14. What applicant's have not shown is a peptide which is capable of stimulating antibodies reactive to SEQ ID NO's: 1-8 but not 9-14. Thus, the specification provides no guidance which leads the artisan to those peptides which more likely than not bind antibodies elevated in schizophrenic patients which bind SEQ ID NO's:1-8 but which do not bind SEQ ID NO's 9-14. The specification does not enable this scope of the claims because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to bind or stimulate antibodies capable of binding SEQ ID NO's:1-8 while also being incapable of binding or stimulating antibodies which do not bind to such highly similar sequences as SEQ ID NO's:9-14. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not expect abrogation of binding amongst such highly homologous, contiguous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed peptides in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, peptides which bind antibodies that are found in elevated levels in body fluids of schizophrenic patients, and are capable of binding to antibodies which do not bind to peptides of SEQ ID NO:9-14 can not be made as the peptide/antibody interaction is unpredictable and the experimentation left to those

skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

In addition, p. 14-16 teach that it is not possible to use the noted proteins to discriminate between a plasma sample obtained from schizophrenic vs. nonschizophrenic patients, and that the sample must be obtained from platelet-derived autoantibodies. Thus, as applicant's claims are not limited to platelet-derived (auto)antibodies, the peptides, method of assay and kit are not commensurate in scope with the enablement provided by the specification.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishiguro et al., Infection and Immunity, 60(4):1550-1557, April 1992, (IDS reference AG). Ishiguro teaches enolase peptides as disclosed in Figure 7, which peptides share a 5-mer segment with instant SEQ ID NO:2, in particular the amino acid sequence "QIKTG". Thus, the peptides would be recognized by the artisan as an immunogen and epitope capable of binding antibodies that bind SEQ ID NO:2 and which are found in elevated levels in body fluids of schizophrenic patients, see in particular Applicant's disclosure, p. 14, line 21. The immunoblotting procedure uses an alkaline phosphatase

conjugated goat-anti-human immunoglobulin. The peptide is immobilized on a solid support for immunoblotting, see in particular 1551, column 1, lines 14-34 and Figure 8. The peptide is reactive with human immunoglobulin, see in particular Abstract, p. 1550, column 2, lines 21-26, Human sera and Figure 8. The reference provides the required reagents and instructions to perform the immunoblotting analysis. It is noted that MPEP 2111.02 discusses the weight of the preamble, specifically the weight given to a preamble statement reciting purpose or intended use as in claim 14. Claim 14 recites a kit "for use in the diagnosis of schizophrenia." However, the preamble fails to structurally delimit the kit by the recitation of a specific product, apparatus or manipulative step which distinguishes the claimed kit from the prior art reagents and methods of analysis. The preamble is not granted patentable weight with respect to the claim because the prior art reagents and methods are similarly capable of performing the intended use as recited in the preamble. Thus, the reference teachings anticipate the claimed peptides and kit as claimed.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Russell et al., Biochem J., 236:115-126, 1986. Russell et al., teach chicken skeletal-muscle enolase peptide with an amino acid sequence which shares a 7-mer sequence with instant SEQ ID NO:2, see in particular residues 1-7 of SEQ ID NO:2 corresponding to residues 383-389 of chicken enolase. The peptide is immunogenic as it is greater than 3 amino acids in length and shares at least a single epitope with SEQ ID NO:2 as the shared sequences is at least 4-6 amino acids in length. Therefore, the peptide is

necessarily capable of binding to an antibody capable of binding to SEQ ID NO:2 and the reference teachings anticipate the claimed invention.

***Status of Claims***

No claims are allowed.

***Allowable Subject Matter***

Claims 5-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The peptide of SEQ ID NO:2 is free of the prior art of record.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
July 8, 2002